Clinical Outcome of Low Birthweight, Long-Term Consequences


Iron and Other Micronutrient Deficiencies in Low-Birthweight Infants

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Abstract
Low birthweight (LBW), defined as birthweight <2,500 g, is a major global public health problem and is associated with lifelong cognitive and behavioral problems. Very LBW (VLBW) infants (<1,500 g) are at high risk of multiple macro- and micronutrient deficiencies, but most LBW infants are larger (1,500–2,500 g), and the most common nutritional problem of those infants is iron deficiency (ID). Globally, about 25% of pre-school children have ID anemia (IDA), the most severe form of ID, and there is good evidence that ID is associated with impaired brain development. However, adverse effects of excessive iron supplementation have been observed. Delayed umbilical cord clamping, which increases infant iron stores, should be recommended for all newborns. There is good evidence that intakes of 2 mg of dietary iron per kg daily prevents IDA in LBW infants without causing adverse effects. A recent study shows that this dose of iron supplementation also reduces the risk of behavioral problems at 3 years in infants with birthweights 2,000–2,500 g. VLBW infants need 2–3 mg/kg per day. To achieve these intakes, breastfed LBW infants should receive iron supplements, and formula-fed LBW infants should receive an iron-fortified infant formula.
imize later morbidity in LBW infants. However, there is still a severe lack of knowledge on this subject – not least with regard to micronutrients – and, consequently, a large variation in nutritional practices.

LBW infants include both term, small-for-gestational-age infants and pre-term infants. Most LBW infants have only marginally or moderately LBW (1,500–2,500 g). Recent advances in neonatal care have significantly improved the survival of very LBW (VLBW) infants (<1,500 g), who are at high risk of multiple macro- and micronutrient deficiencies. However, this review will mainly focus on the larger LBW infants, and the most common nutritional problem of those infants is iron deficiency (ID).

**Iron Deficiency**

ID is the most common single-nutrient deficiency worldwide [4]. Young children, and especially LBW infants are at high risk of ID since their rapid growth leads to high iron requirements. Globally, about 25% of pre-school children are estimated to have ID anemia (IDA), the most severe form of ID, and the highest prevalence is found in South Asia and Africa, where up to 50% of young children have IDA in socioeconomically disadvantaged areas [4]. In Europe, the prevalence of IDA in toddlers is 3–4% in the general population [5] but much higher in subpopulations at risk, including those with LBW.

Growth and development of the central nervous system is rapid during the first years of life, and iron is critical for this process. The human brain almost triples its weight from birth to 3 years of age, and has at that age reached 85% of its adult size. Animal studies have shown that iron is required for several aspects of brain development: myelination, monoamine neurotransmitter function and neuronal and glial energy metabolism [6].

Several well-performed case-control studies in children have shown a consistent association between IDA in infancy and long-lasting poor cognitive and behavioral performance [7]. In summary, even though there still is limited data from human intervention studies [8], the available evidence suggests that it is important to prevent ID in infants to ensure optimal neurodevelopment.

However, it is important to note that iron, in contrast to most other nutrients, cannot be actively excreted by humans, and the risk of iron overload must therefore be considered. We and others have shown that iron supplementation of iron replete infants may have adverse effects, e.g. increased risk of infection and impaired growth [9]. Increased risk of severe infections seems to be restricted to malarious regions (see below), while the risk of impaired growth has been observed also in European infants [10, 11]. A single study has even suggested that
a high iron intake may have adverse effects on long-term cognitive outcomes in iron-replete infants [12]. Furthermore, iron is a potent pro-oxidant, and non-protein-bound iron has been suggested to cause formation of reactive oxygen species, especially in newborns before 2 weeks of age, and possibly increase the risk for e.g. retinopathy of prematurity [13, 14].

It is therefore important to identify iron requirements in infants to avoid both ID and iron overload.

**Estimated Iron Requirements**

At birth, most of the body iron is found in blood hemoglobin (Hb), but a term, healthy, normal-birthweight infant also has some iron stores, corresponding to about 25% of total body iron (fig. 1). When the newborn emerges from the relatively hypoxic environment of the uterus out into the oxygen-rich atmosphere, Hb synthesis is halted, and the Hb falls from an average of 170 g/l to about 120 g/l during the first 6 weeks of life [9]. Due to recirculation of iron from senescent erythrocytes, iron is transferred from Hb to iron stores, which thereby increase in size. During the following months, as the baby continues to grow and expand its blood volume, iron is transferred back from stores to the blood compartment, making the normal infant virtually self-sufficient with regard to iron during the first 6 months of life (fig. 1). This is compatible with the very low concentration of iron in breast milk (0.3 mg/l).
LBW infants clearly have lower iron stores due to their lower bodyweight. The body iron content at birth has been calculated to be 75 mg/kg at weights ranging between 0.2 and 4 kg, based on fetal body composition studies from the 1950s [15]. As shown in figures 2 and 3, LBW infants have higher iron requirements during the first months of life due to more rapid postnatal growth. Based on expected growth and assuming negligible iron losses, the increase in total body iron corresponds to dietary iron requirements of 1–2 mg/kg per day between 6 weeks and 6 months of age in an LBW infant with a birthweight of 2,000 g.
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201 g (fig. 2), and 2–3 mg/kg per day between 2 weeks and 6 months of age in a VLBW infant with a birthweight of 1,000 g (fig. 3). These conclusions are compatible with previous calculations using a similar factorial approach when iron requirements for VLBW infants have been estimated to be about 2 mg/kg per day over the course of the first 12 months of life [16].

The timing of umbilical cord clamping is of great importance for the amount of blood transfused from the placenta to the newborn. We and others have shown that delayed cord clamping increases iron stores and prevents ID at 3–6 months of age in normal-birthweight infants [17, 18]. This may be even more important in preterm infants. A Cochrane review concluded that delayed cord clamping of preterm infants was associated with less need for blood transfusions [19].

In VLBW infants, blood losses and blood transfusions related to neonatal intensive care will greatly influence iron status and iron requirements. Iron losses due to phlebotomy have been estimated to be 6 mg/kg per week [20]. On the other hand, each red blood cell transfusion typically adds 8 mg/kg of iron. Hepatic iron stores as well as serum ferritin concentrations in preterm infants are highly correlated with the number of blood transfusions received [21]. Erythropoietin treatment results in greatly increased iron requirements, and high doses of oral or parenteral iron is recommended as an adjunct to this therapy. Thus, local practice regarding blood sampling, blood transfusions and erythropoietin treatment will greatly influence iron requirements of VLBW infants. It is useful to follow serum ferritin concentrations in infants who have received multiple blood transfusions to assure that they do not develop iron overload.

In normal birthweight infants, virtually no external iron is required during the first 6 months of life, but dietary iron requirements are high at 6–24 months of age, corresponding to about 0.1 mg/kg per day of absorbed iron or 1 mg/kg per day of dietary iron, assuming a fractional absorption of 10% [22]. Assuming an optimal diet and normal growth, LBW infants should have similar iron requirements as normal-birthweight infants after 6 months corrected age.

Effects of Interventions

There are relatively few published randomized intervention trials comparing different doses of iron supplements or fortification of human milk or formula given to LBW infants.

A meta-analysis has shown that prophylactic iron at a dose of 2 mg/kg per day given to LBW infants, most of which with birthweights 1,500–2,500 g, leads to significantly reduced incidence of anemia at 6 months [23].
In a study by Friel et al. [24], 58 infants with an average birthweight of 1,500 g were randomized to different infant formulas resulting in iron intakes of 3–6 versus 2–3 mg/kg per day up to 9 months of age. There was no difference in anemia or neurodevelopment at 12 months. However, the high-iron group had higher glutathione peroxidase concentrations (a marker of oxidative stress), lower plasma zinc and copper levels and a higher number of respiratory tract infections, suggesting possible adverse effects with the higher iron intakes.

It is not clear at what postnatal age iron supplements should be initiated in order to prevent ID in LBW infants. Two randomized trials in VLBW infants with an average birthweight of 0.9–1.2 kg have shown that early initiation of iron supplementation or fortification (2 weeks postpartum, compared to 6–8 weeks) may reduce the need of blood transfusions [25, 26].

**Iron Requirements of Marginally LBW Infants**

We have recently performed a randomized, controlled, blinded trial (n = 285) of iron supplements at the following doses: 0 (placebo), 1 or 2 mg/kg per day, given from 6 weeks of age to 6 months of age in a population of otherwise healthy Swedish marginally LBW infants with birthweights 2,000–2,500 g.

We could show that iron supplements at a dose of 2 mg/kg per day, compared to placebo, significantly reduced the risk of IDA at 6 months [27]. In the placebo group, 36% developed ID and 10% developed IDA, as compared to 4 and 0% in the 2 mg group. About half of these infants were mostly breastfed during the intervention and the other half received iron-fortified formula. No adverse effects of iron supplements were observed with regard to infant growth, infections or other morbidity. There were significant differences in iron status between those who had received 1 or 2 mg/kg per day of iron but there were no significant differences in the proportion of infants with ID or IDA in those two groups. When considering all dietary iron sources and iron supplements, including compliance, we could show that an actual iron intake of 0.25 mg/kg per day was sufficient to prevent IDA, and an intake of 1 mg/kg per day prevented ID [27].

Interestingly, when we followed up the LBW children from the above RCT at 3.5 years of age, we found a significantly higher proportion of abnormal behavioral scores in the placebo group [28]. Using a validated questionnaire (Achenbach Child Behavior Checklist), the prevalence of children with behavioral scores above the US subclinical cutoff was 12.7, 2.9 and 2.7% in the placebo, 1 mg, 2 mg, and control group respectively, as compared to 3.2% in a reference group of children with normal birthweight. Adjusting for socioeconomic con-
founders, the risk of behavioral problems was 4.5 times higher (95% CI: 1.3–15.8) in placebo-treated compared to iron-supplemented children. However, no significant differences were observed in cognitive scores.

**International and National Recommendations for Iron Intake in LBW Infants**

The WHO previously recommended 2 mg/kg per day of iron from 2–23 months of age for all LBW infants [29], and more recently recommended 2–3 mg/kg per day from 6–8 weeks to 12 months of age [30]. The American Academy of Pediatrics recommends 2 mg/kg per day from 1–12 months to breastfed LBW infants [31]. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition recommends 2–3 mg/kg per day from 2–6 weeks to 6–12 months.

**Iron Supplements in Malaria-Endemic Areas**

Supplementation with iron, which is an essential nutrient also for pathogens, may increase the risk of diarrhea and malaria [32, 33].

In 2003, a large RCT of iron supplementation in Pemba, Tanzania, which has a high prevalence of malaria, had to be terminated due to serious adverse effects [10]. In this trial, 24,000 children aged 1–35 months were randomized to daily oral supplementation with iron (12.5 mg) and folic acid or placebo. The dose of iron was halved in infants <12 months. In the groups receiving iron and folic acid, there was a 15% increased risk of death and an 11% increased risk of hospital admission. A substudy suggested that the risk for serious adverse events was higher in infants who were initially iron replete, i.e. those with higher Hb and lower zinc protoporphyrin. A similar study performed in Nepal showed that such adverse effects are not observed in a non-malarious region [34].

This led to a joint statement by the World Health Organization and the United Nations Children’s Fund in 2007 advising that, in regions with high prevalence of malaria and other infections, iron/folic acid supplementation should be limited to those identified as iron deficient [35]. A more recent Cochrane review in 2011 concluded that iron supplementation alone or with antimalaria treatment does not increase the risk of clinical malaria or death when regular malaria surveillance and treatment services are provided [36]. However, such services are not generally available in all low-income countries.

Since LBW infants are at high risk of ID, and can be assumed not to be iron replete, the risk of adverse effects is likely to be lower, and iron supplements can be recommended for this patient group, preferably of course in combination with
malaria surveillance and treatment. If breast milk is not available, iron-fortified infant formula is a good option, since it has not been associated with increased risk of malaria.

**Other Micronutrient Deficiencies in LBW Infants**

Similarly to normal-birthweight infants, LBW infants are at risk of deficiencies of vitamin K and vitamin D, and should therefore receive prophylactic vitamin K soon after birth and vitamin D supplementation during infancy if they do not receive a vitamin D-fortified infant formula.

VLBW infants have extraordinarily high macro- and micronutrient requirements and a high risk of general malnutrition, severe growth failure, visual impairment and cognitive/behavioral problems. Recent studies have suggested that low macronutrient intakes, especially protein and energy, during the early postnatal period are associated with poor neurodevelopment and retinopathy of prematurity, a major cause of visual impairment and blindness in VLBW children [37, 38]. Micronutrient deficiencies are also common in these infants, and clinical deficiencies of sodium, calcium, phosphorus, iron, zinc, copper, vitamin A, vitamin D, vitamin E, vitamin K, riboflavin and folic acid have all been described in this patient group [39]. Even in modern neonatal units, where micronutrient supplemented parenteral and enteral nutrition is routinely used, it is difficult to achieve recommended intakes of macro- and micronutrients [40]. Preliminary data from a population-based Swedish cohort of extremely preterm infants born 2004–2007 showed that average intakes during the first 4 weeks of life were lower than recommended for calcium, phosphorous, zinc, copper, iodine and magnesium [unpubl. data]. Such suboptimal micronutrient intakes may have negative short- and long-term effects on growth, bone health and immune function even though this has not been sufficiently studied.

**Conclusions**

LBW infants are at risk of ID, which is associated with impaired brain development and later behavioral and cognitive problems. Delayed umbilical cord clamping, which increases infant iron stores, should be recommended for all newborns, including LBW infants. There is good evidence that intakes of 2 mg of dietary iron per kg daily starting at 2–6 weeks of age prevent IDA in LBW infants without causing adverse effects. VLBW infants need 2–3 mg/kg per day starting at 2 weeks of age. To achieve these intakes, breastfed LBW infants should receive iron supplements,
and formula-fed LBW infants should receive an infant formula fortified with iron to a concentration of approximately 12 mg/l. Iron supplements should be continued up to 6–12 months of age, depending on the diet and growth of the infant and the local prevalence of IDA. After discontinuation of supplements, LBW infants should follow dietary recommendations for normal-birthweight infants.

**Disclosure Statement**

The author declares that no financial or other conflict of interest exists in relation to the content of the chapter.

**References**